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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/647,522	12/01/2000	Hiroshi Nagai	1830/49264	8049

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EXAMINER

SCHNIZER, HOLLY G

ART UNIT	PAPER NUMBER
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1653

DATE MAILED: 06/14/2002

8

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Application No.

09/647,522

Applicant(s)

NAGAI ET AL.

Examiner

Art Unit

Holly Schnizer

1653

Office Action Summary*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --***Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 18 April 2002.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 17-36 is/are pending in the application.
- 4a) Of the above claim(s) 19-21,23-31 and 33-35 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 17,18,22,32 and 36 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
 - a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ . |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ . | 6) <input type="checkbox"/> Other: _____ . |

DETAILED ACTION

Status of the Claims

The Response to the Restriction Requirement filed April 18, 2002 (Paper No. 7) has been entered and considered. Claims 17-36 are pending. Claims 19-21, 23-31, and 33-35 are withdrawn from consideration as being drawn to a non-elected invention for the reasons explained below. Claims 17, 18, 22, 32, and 36 have been considered in this Office Action.

Election/Restrictions

Applicant's election with traverse of Group I, Claims 17-18, 22, 32, and 36 in Paper No. 7 is acknowledged. The traversal is on the ground(s) that there is no serious burden to search the groups together and, specifically, that a search of the cDNA would overlap a search of the protein encoded by the corresponding cDNA. This is not found persuasive because the present application is a 371 of PCT/JP99/01607 and Unity of Invention was determined according to 37 C.F.R. 1.475. According to 37 C.F.R. 1.475(a), a national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept. 37 C.F.R. 1.475(b) states that a "special technical feature" is a technical feature that defines a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. As stated in the previous Office Action, the technical feature linking the inventions of Groups I-V does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art because Allison et al. (Infect.

Immun. (July 1997) Vol. 65(7): pp. 2765-2771) teaches a hemolysin that has hemolytic activity (see abstract). (It is noted that the claims are drawn to polypeptides having hemolytic activity wherein the polypeptide may have any number of amino acid substitutions, deletions, or additions). Therefore, the claimed polypeptides are not distinguishable from those of Allison et al.

The examiner will rejoin the polypeptide sequences of SEQ ID NOs: 1, 2, 3, and 5 since SEQ ID NOs: 1, 2, and 3 are short sequences within SEQ ID NO:5.

The requirement is still deemed proper and is therefore made FINAL.

Priority

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). For example, a statement reading "This Application is a 371 of PCT/JP99/01607, filed March 30, 1999" should be entered following the title of the invention or as the first sentence of the specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 17, 18, 32, and 36 rejected under 35 U.S.C. 102(b) as being anticipated by Allison et al. (*Infect. Immun.* (1997) p. 2765-2771; cited in Paper No. 6).

Allison et al. teach the isolation of a protein that has hemolytic activity (see abstract and p. 2766, Col. 2, 5th full paragraph). While the protein disclosed in Allison et al. does not appear to have an identical amino acid sequence as SEQ ID NO:1, 2, 3 or 5, it is considered to be at least one of these sequences modified by additions, deletions, and substitutions. Since the present specification does not provide any sequence characteristics that distinguish hemolytic proteins of *Carybdea rastonii* from those isolated from other sources, it appears that the protein of Allison et al. is patentably indistinguishable from that of Claim 18. The protein of Allison et al. is contained in purified form in a composition, and is therefore considered to be patentably indistinguishable from the compositions of Claims 32 and 36 since the only component of the compositions claimed therein appears to be a hemolytic protein. Thus, the claims are unpatentably over Allison et al.

Claims 17, 18, 32, and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by Sato (*Ochanomizu Igaku Zasshi* (1985) 33(2) 131-151 (abstract) Toxcenter [Bioscience on STN] Retrieved from: STN International, Columbus, OH, USA. Accession Number CA10321175714H).

Sato teaches a protein isolated from the tentacles of *Carybdea rastonii* with hemolytic activity (see abstract). The protein disclosed in Sato is isolated from the same source, has the same activity, and the same molecular weight (50,000 daltons) as

that of the present invention. Therefore, the Sato protein is considered, at least, to comprise one of the claimed sequences modified by an addition, deletion, and/or substitution. Since the only components of the compositions of Claims 32 and 36 are the hemolytic protein of claim 17, the composition containing the protein disclosed in Sato is considered to be patentably indistinguishable from the compositions of Claims 32 and 36.

Claims 17, 18, 32, and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by Tamkun et al. (*Biochim. Biophys Acta* (1981) 667: 87-98).

Tamkun et al. a hemolytic protein isolated from the nematocyst venom of the Portuguese Man-of-War (see entire document and p. 95, "Discussion" for activity). The protein disclosed in Tamkun et al. is considered to comprise the sequence of SEQ ID NO:5, modified by amino acid additions, deletions, and substitutions. In the absence of any characteristics that identify a protein as isolated from a nematocyst of *Carybdea rastonii*, it appears that the protein of Tamkun et al. is patentably indistinguishable from that of Claim 18. Since the only product recited in the compositions of Claims 32 and 36 is the protein of Claim 17, the protein compositions of Tamkun et al. are considered to meet the limitations of these claims. Thus, the claims appear to be anticipated by Tamkun et al.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

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art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17, 18, 22, 32, and 36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated protein comprising the amino acid sequence of SEQ ID NO:5 wherein said protein has hemolytic activity, does not reasonably provide enablement for an isolated protein comprising the amino acid sequence of SEQ ID NOs: 1-3, or SEQ ID NOs: 1-3 and 5 modified by any number of additions, deletions, and/or substitutions wherein said protein has hemolytic activity; or pharmaceutical or pesticide compositions comprising the proteins; or an isolated protein produced by expression of a polynucleotide that hybridizes with a polynucleotide encoding the amino acid sequence of SEQ ID NO: 1-3 or 5. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. In the instant case, practicing the claimed invention commensurate in scope with the claims would require undue experimentation. Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F2d, 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include (1) quantity of experimentation, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Breadth of the Claims

Since Claim 17 is unlimited in the number and position of amino acid additions, deletions, and substitutions that can be made to SEQ ID NOs: 1-3 or 5, it is considered to encompass any protein of any sequence having hemolytic activity. Claims 32 and 36 depend from this claim and include the intended use of the protein of Claim 17 as a pharmaceutical or pesticide.

Since there is no known characteristic sequence of hemolytic proteins of *Carybdea rastonii*, Claim 18, is considered to encompass any protein of any sequence having hemolytic activity.

Claim 22 encompasses any protein having any activity that is produced by expression of a polynucleotide sequence encoding SEQ ID NO:1-3 or 5 or a polynucleotide which hybridizes to the polynucleotide encoding SEQ ID NOs: 1-3 or 5. Given the appropriate conditions, hybridization can occur between completely unrelated polynucleotide sequences. Therefore, this claim encompasses proteins having an infinite number of sequences and functions.

Amount of Direction or guidance presented/ presence or absence of working examples

The present Specification describes and provides working examples of the isolation, sequencing, and determination of function of a full-length protein of SEQ ID NO:5 isolated from *C. rastonii*. The function of the short peptides (14-16 amino acids in length) of SEQ ID NOs: 1-3 is not disclosed and the Specification does not indicate that these short peptides maintain the hemolytic activity of the full-length protein. After the protein of the invention was isolated, the sequences of these peptides (SEQ ID NOs: 1-

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3) appear to have been used as tools to obtain the sequence of the full length cDNA encoding the protein of the invention and the specification does not provide any further guidance or examples as to the functions of the individual peptides. The present Specification does not provide any guidance or examples of using the claimed proteins as a pharmaceutical or as a pesticide. The present Specification does not teach how the claimed proteins function in hemolysis (e.g. catalytic function or binding function) and does not even teach whether or not the hemolytic activity observed correlates with the toxicity of jellyfish stings. While there is no requirement that the Specification teach the biochemical function that results in hemolysis, in the present case, such information would be essential to understanding whether or not the hemolytic activity causes the toxicity of the jelly fish sting rather than another activity the protein may have.

Nature of the Invention

The invention involves the discovery of a single protein (SEQ ID NO:5) isolated from *C. rastonii* that appears to have hemolytic activity. The Specification asserts that the proteins described therein can be used to develop medicine for treating jellyfish stings, or as a drug with platelet agglutination effect or as a pesticide. However, the Specification does not teach how the proteins would be used in these methods. The nature of the claimed invention involves prediction of protein function from a single unique amino acid sequence with unknown biochemical activity, the use of this protein and unknown related proteins in the treatments and pesticides.

Predictability/Unpredictability

Merely predicting protein function from amino acid sequence information is considered highly unpredictable as evidenced by Smith et al. (Nature Biotechnol. (1997) 15: 1222-1223), Doerks et al. (Trends in Genetics (1998) 14(6) : 248-250), and Zhang et al. (Proc. Natl. Acad. Sci. (2000) 97(6): 2550-2555). In fact, Smith et al. Doerks et al. discuss the difficulties and common errors in attempting to predict the function of a given protein based on its amino acid sequence similarity to other proteins of known function. The present case would be even more difficult than those discussed in Smith et al. and Doerks et al. because the sequence of the protein of the present invention does not appear to be closely related to any other known protein. Moreover, the Specification does not provide guidance as to the biochemical function that results in hemolysis. Therefore, one of skill in the art would not have any basis to predict what affect changing any particular amino acid residue would have on protein function. Moreover, since function requires a particular protein structure and since protein structure depends on amino acid residues throughout the protein sequence (e.g. a protein fold may involve contacting two cysteines on either end of the protein sequence), one of skill in the art would not expect that a short peptide of 14-16 amino acids would maintain the function of the corresponding full length, 450 amino acid, protein. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function

relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions. The instant claims encompass proteins with any number of amino acid substitutions, deletions, or additions. However, Applicant has provided no guidance beyond the mere disclosure of a single, naturally occurring protein to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions, additions or deletions), and the nature and extent of changes that can be made in these positions. While one of skill in the art may know how to screen proteins for hemolytic activity, this is not adequate guidance as to the nature of the proteins that may be constructed, but is merely an invitation to the artisan to use the disclosed protein as a starting point for further experimentation.

State of the Prior Art and Relative Skill in the Art

A thorough search of the prior art indicates that at the time of the invention, a protein with sequence similar to that of SEQ ID NO:5 was unknown. There were no known pharmaceuticals containing a related protein from the toxins of jellyfish that were used to treat jellyfish stings. In fact, Nagai et al. state that the mode of action of jelly fish toxins is not understood and that a better understanding of that mode of action is necessary to permit the development of treatments for jelly fish stings (see Nagai et al. (Biochem. Biophys. Res. Comm. (2000) 275: 582-588). Thus, it appears that further

characterization of the protein was required before those of skill in the art would be able to use the protein in any methods of treatment.

At the time of the invention, there were no known pesticides made from proteins related to the claimed proteins or from other jellyfish toxins. The Specification does not provide guidance as specifically how it would be used and what it would be used for (e.g. killing weeds, insects, funguses, or viruses, etc.?). Thus, it appears that further characterization of the protein would be required before those of skill in the art would be able to use the protein of the invention as a pesticide.

And, as explained above, at the time of the invention, one of skill in the art considered protein function prediction based on amino acid sequence alone highly unpredictable.

Quantity of Experimentation

For the reasons stated above, a large quantity of experimentation would be necessary to generate the infinite number of modified proteins recited in the claims and possibly screen same for hemolytic activity. Moreover, undue experimentation would be required to characterize the peptides of SEQ ID NOs: 1-3 so as to determine their function. To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve the determination of those amino acid residues in the disclosed protein that are required for the functional and structural integrity of the protein. It is this additional characterization of the protein that is required in order to obtain the functional

and structural data needed to permit one to produce a protein which meets both the structural and functional requirements of the instant claims that constitutes undue experimentation.

The examiner notes that this rejection could be overcome by amending the claims to be drawn to an isolated protein comprising the amino acid sequence of SEQ ID NO:5 and/or a composition comprising an isolated protein comprising the amino acid sequence of SEQ ID NO:5.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17, 18, 22, 32, and 36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. .

Applicant is referred to the Written Description Guidelines published January 5, 2001 in the Federal Register, Vol. 66, No. 4, p. 1099-1111 (also available at www.uspto.gov).

The specification does not set forth the invention in terms of distinguishing, identifying characteristics sufficiently detailed to show that applicant was in possession of the claimed invention. The specification does not show 1) what distinguishing, identifying characteristics of the amino acid sequence of SEQ ID NO: 5 provides

hemolytic activity, 2) what distinguishes a protein with hemolytic activity isolated from the nemocyst of *Carybdea rastonii* from hemolytic proteins isolated from other sources, or 3) any distinguishing, identifying characteristics of a protein expressed from a polynucleotide sequence that hybridizes with a polynucleotide sequence encoding SEQ ID NO:1-3, or 5.

Claims 17, 18, and 22 are directed to a genus of proteins of any sequence that either have hemolytic activity (clms. 17 and 18) or a genus of proteins that are encoded by a polynucleotide that hybridizes to the polynucleotide of SEQ ID NOs: 1-3 or 5. The Specification describes one example of a protein from *Carybdea rastonii* with hemolytic activity (SEQ ID NO:5). A search of the sequence database revealed that the structure (sequence) of the protein of the invention was unrelated to any other. Thus, the protein sequence appears to be unique. Since Claims 32 and 36 encompass all of the proteins of Claim 17, they lack written description for the reasons provided for Claim 17.

For a claim drawn to a genus, the written description requirement for the claimed genus may be satisfied through sufficient description of a representative number of identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see Written Description Guidelines, p. 1106, Col. 3, paragraph 2-3).

In the present case, only one species has been described by actual reduction to practice. The single disclosed species in the present case is not sufficient to describe

the genus because the genus is highly variable. The claims encompass any amino acid sequence that gives hemolytic activity or any amino acid sequence encoded by a polynucleotide that hybridizes to the polynucleotides encoding SEQ ID NOs: 1-3 or 5. Since proteins that have hemolytic activity may vary in biochemical function and mechanism causing that hemolytic activity, it would be expected that proteins with hemolytic activity would be highly variable in sequence. Moreover, proteins that can have any function or sequence so long as the polynucleotide encoding them hybridizes to the polynucleotide encoding SEQ ID NO:5 or the short peptides of SEQ ID NO: 1-3 would be infinitely variable.

There are no common attributes that identify proteins as members of the genus. The Specification does not provide any identifying characteristics of hemolytic proteins from *Carybdea rastonii* so as to distinguish them from other hemolytic proteins. The specification is silent as to the specific biochemical function (the biochemical function that results in the hemolytic activity; e.g. binding or catalytic) of the claimed protein and the Specification does not provide guidance as to what effect changing any of the amino acids has on the function of the resulting phenotype. The general knowledge and level of skill in the art do not supplement the omitted description with respect to what amino acids are important. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, SEQ ID NO:5 alone is insufficient to describe the genus. Thus, the claims are not supported by an adequate written description because a representative number of species have not been described.

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The examiner notes that amending the claims to be directed to an isolated protein comprising the amino acid sequence of SEQ ID NO:5 or a composition comprising an isolated protein comprising the amino acid sequence of SEQ ID NO:5 would overcome this rejection.

Conclusion

No Claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (703) 305-3722. The examiner can normally be reached on Mon. & Thurs., 8am-5:30pm and Tues. & Wed. 9am-2:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.


Holly Schnizer
June 14, 2002


CHRISTOPHER S. F. LOW
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